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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/032,393	12/21/2001	Robert Haselbeck	ELITRA.010A	5173

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EXAMINER	
VOGEL, NANCY S	

ART UNIT	PAPER NUMBER
1636	

DATE MAILED: 03/10/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

H/L

Office Action Summary	Application No.	Applicant(s)	
	10/032,393	HASELBECK ET AL.	
	Examiner	Art Unit	
	Nancy T. Vogel	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *06 December 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-143* is/are pending in the application.

4a) Of the above claim(s) *12,23,48-135 and 143* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-11,13-22,24-47 and 136-143* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *21 December 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *4/12/04 & 12/6/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 1-143 are pending in the case.

Receipt of Information disclosure statements filed 4/12/04 and 12/6/04 is hereby acknowledged. References which are duplicates have been struck through.

Election/Restrictions

Claims 12, 23, 41 and 48-135 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 3/25/04.

Response to Amendment

Any rejection of record in the previous action not addressed in this office action is withdrawn.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1, 7, 9, and 10 are rejected under 35 U.S.C. 102(b) as being anticipated by Geissendorfer et al. (Appl. Microbiol. Biotechnol., 33:657-663, 1990) (newly cited).

Geissendorfer et al. disclose isolated nucleic acids comprising a fusion promoter said fusion promoter comprising at least one promoter comprising at least one nucleotide sequence modification which alters the transcriptional activity of said promoter in at least one gram-positive organism said promoter being linked to at least one operator, wherein said at least one operator is positioned such that binding of at least one repressor to said at least one operator represses transcription from said fusion promoter. The reference discloses an embodiment in which the *tet* promoter of Tn*10* is altered by adding a poly A block upstream of the –35 region, the *tet* operator (*tetO*) is maintained, and the homology of the promoter to the consensus sequences for *B. subtilis* promoters is increased to increase promoter strength (see Figs. 1 and 2, pWH346 discussed first and second column of page 659). The reference discloses an embodiment in which the *tet* operator sequence was placed between the –35 and –10 boxes of the xylose promoter region (see Fig. 3, *xyl/tet* fusion promoter, pWH353). The reference discloses this fusion promoter, with a second *tet* operator (pWH354).

It is noted that since the claim 1 recites that the at least one promoter has "at least one nucleotide sequence modification which alters the transcriptional activity of said promoter", the nucleotide sequence of the resultant "altered" promoter encompasses **any** promoter sequence, since one can produce any sequence from any other by altering the nucleotide sequence.

Claim 1, 7, 9, 10 and 136-143 are rejected under 35 U.S.C. 102(b) as being anticipated by Marra et al. (WO 99/28508) (cited by applicants).

This rejection is maintained essentially for the reasons made of record in the previous Office action, with modification necessitated by applicant's amendments.

Applicants have argued that they have reviewed the reference, and have found that Marra et al. do not disclose a promoter which comprises a nucleotide sequence modification that alters the transcriptional activity of the promoter in a gram-positive organism. However, as has been argued above, the phrase "at least one promoter comprising at least one nucleotide sequence modification which alters the transcriptional activity of said promoter" encompasses any promoter sequence, since one can produce any sequence from any other by altering the nucleotide sequence. Marra et al. disclose said promoter operably linked to a nucleic acid which encodes an antisense nucleic acid that inhibits the expression of a gene which encodes a gene product required for the proliferation of said at least one gram-positive organism, and vectors and host cells comprising said promoter (see pages 4, 5, 13-17, and claims)

Claim Rejections - 35 USC § 103

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 1-4, 7-11, 13-15, 18-22, 24-27, 29, 32,33, 36-40, 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. (EP 0186 069) in view of Sizemore et al. (J. Bacteriol. 174 (9):3042-3048) (both previously cited).

This rejection is maintained for the reasons made of record in the previous Office action.

Applicant has argued in the response filed 12/6/04 that neither Bujard et al. nor Sizemore et al. disclose a promoter that comprises at least one nucleotide sequence modification which alters the transcriptional activity of the promoter in a gram-positive organism (page 29). Further, applicants argue that there was no motivation to combine the disclosure of Bujard et al. with Sizemore et al. "nor would a skilled artisan reasonably expect a promoter from a gram-negative organism fused to an operator from a gram-positive organism to promote regulatable transcription in an organism" (page 29). However, it is maintained that Bujard et al. discloses that the host microorganism may be any gram negative or gram postive bacteria (see column 5, first complete paragraph, and claims), and therefore, one of skill in the art would have expected that the promoter disclosed by Bujard et al. would be functional in hosts such as *S. aureus*. It was well known at the time of the instant invention that the operator element is a cis regulatory element that is recognized by a trans acting repressor protein present in a host cell, and therefore, one would have expected success in utilizing the known *xylO* operator element of a staphylococcus microorganism, when using said staphylococcus microorganism as a host cell. Regarding applicants' argument that Bujard et al. does not disclose a promoter comprising "at least one nucleotide modification which alters the

transcriptional activity of said promoter in at least one gram-positive organism", it is maintained that the fusion of the *xylO* operator to the promoter meets this limitation of the claims. It is noted that the elected species, i.e. SEQ ID NO:36 does not contain any difference in its nucleotide sequence when compared to that of Bujard et al. (see attached sequence alignment), and therefore, the claim has been interpreted in the broadest reasonable terms, i.e. that the alteration recited is the addition of the *xylO* operator. Since the borders of a "promoter" are not absolute, the fusion between nucleotides of the promoter with the *xylO* element, constitutes an "alteration" to the promoter. Furthermore, as has been argued in the previous rejections, the phrase "at least one promoter comprising at least one nucleotide sequence modification which alters the transcriptional activity of said promoter" encompasses any promoter sequence, since one can produce any sequence from any other by altering the nucleotide sequence. Therefore, applicants' arguments are not found convincing.

Claims 1-4, 7-11, 13-15, 18-22, 24-29, 32, 33, 36-40, 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. (EP 0186 069) (cited by applicants) in view of Sizemore et al. (J. Bacteriol. 174 (9): 3042-3048) as applied to claims 1-4, 7-11, 13-15, 18-22, 24-27, 29, 32, 33, 36-40, 42-47 above, and further in view of Shih et al. (US Patent 4,959,311), Kisumi et al (US Patent 4,656,136) or Pederson et al. (Molecular and General Genetics, 244 (4): 374-382 (1994).

This rejection is maintained for the reasons made of record in the previous Office action mailed 5/24/04.

Applicants have repeated their arguments set forth above, i.e. that the cited references taken in combination do not disclose at least one nucleotide sequence modification which alters the transcriptional activity of said promoter in at least one gram-positive organism, and that one would not have been motivated to combine a T5 promoter with a *xyl* operator. For the reasons set forth in the above response, applicants' arguments have not been found convincing.

Claims 1-11, 13-27, 29, 32-40, 42-47 rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard (EP 0186 069) in view of Sizemore et al. as applied to claims 1-4, 7-11, 13-15, 18-22, 24-27, 29, 32, 33, 36-40, 42-47 above, and further in view of Bujard et al. (US Patent 5,362,646).

Applicants have repeated their arguments set forth above, i.e. that the cited references taken in combination do not disclose at least one nucleotide sequence modification which alters the transcriptional activity of said promoter in at least one gram-positive organism, and that one would not have been motivated to combine a T5 promoter with a *xyl* operator. For the reasons set forth in the above response, applicants' arguments have not been found convincing.

Claims 1-4, 7-11, 13-15, 18-22, 24-27, 29-33, 36-40, 42-47 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. (EP 0186 069) (cited by applicants) in view of Sizemore et al. (J. Bacteriol. 174 (9): 3042-3048) as applied to claims 1-4, 7-11, 13-15, 18-22, 24-27, 29, 32, 33, 36-40, 42-47 above, and further in

view of Israelson et al, (Appl. Environ. Microbiol. 61: 2540-2547 (1995)(cited by applicants).

Applicants have repeated their arguments set forth above, i.e. that the cited references taken in combination do not disclose at least one nucleotide sequence modification which alters the transcriptional activity of said promoter in at least one gram-positive organism, and that one would not have been motivated to combine a T5 promoter with a *xyl* operator. For the reasons set forth in the above response, applicants' arguments have not been found convincing.

Claims 136-143 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bujard et al. (EP 0186 069) in view of Sizemore et al. (J. Bacteriol. 174 (9):3042-3048) (both previously cited), and further in view of Ji et al. (J. Bacteriol. 181 (21, 6585-6590, 1999) and Kernodle et al. (Infect. Immun. 65 (1), 179-184, 1997).

Bujard et al. disclose an isolated nucleic acid comprising a fusion promoter comprising the T5 promoter operatively linked to a heterologous operator permitting the control of the promoter activity. The reference discloses that any operator/repressor system may be used (see col. 3-4 and claims). The reference discloses the lacO region linked to the T5 promoter. The fusion promoter is responsive to an inducer (col. 12, example 4). The reference discloses the promoter linked to a reporter gene, contained in a vector, and a host cell comprising the promoter (see Example 4). The difference between the reference and the instant claims is that the xylO operator is linked to the T5 promoter, the host cell is S. aureus, and the fusion promoter is operably linked to a

nucleic acid which when transcribed produces an antisense nucleic acid that inhibits the expression of a gene which encodes a gene product required for the proliferation of at least one gram-positive organism.

However, Sizemore et al. disclose nucleic acids comprising the xylose utilization control region for S. xylosus, including the operator region (see Fig. 1, and pages 3043-3044, and page 3047, first column). The reference discloses that the control region is induced by xylose. The reference discloses the vectors comprising said nucleic acids, and staphylococcus microorganisms comprising said nucleic acids (see pages 3043-3044. Ji et al. disclose constructs comprising the tet promoter system operably linked to a nucleotide sequence which encodes a gene product involved in the virulence of a gram-positive microorganism i.e. S. aureus (see page 6585, second column, see page 6588, discussion section). Kernodle et al. disclose constructs comprising a promoter linked to a nucleic acid which when transcribed produces an antisense nucleic acid that inhibits the expression of a gene, and further discloses said antisense nucleic acid may encode a gene that is required for a bacteria to live, including constructs wherein the expression of the antisense DNA fragment reduces the production of the protein encoded by the gene without eliminating it completely. The reduced levels of production may be sufficient for the microbe to survive, albeit in a weakened form, allowing the attenuation of microbes (see page 182, second column).

It would have been obvious to one of ordinary skill in the art to have substituted the xylO operator from a staphylococcus microorganism, for the lacO region in the fusion promoter disclosed by Bujard et al., since both references disclose prokaryotic

expression control regions, made up of a promoter and an operator region, and since Bujard et al. disclose that it is possible to combine the T5 promoter with a heterologous operator, such as that of the lac operon or any other operon, in order to control expression of an operably linked nucleic acid using the native inducer of that operon. It would have been further obvious to one of ordinary skill in the art to have operably linked a nucleic acid encoding an antisense nucleic acid that inhibits the expression of a gene required for bacterial survival, as disclosed by Ji et al. and Kernodle et al, since these reference disclose the use of regulated promoters for the production of nucleic acids and proteins of interest in gram-positive host cells. One would have been motivated to make the above substitution by the known equivalence of functions of the lac and xyl operator regions, and the know usefulness of the xylO operator region in controlling gene expression, inducible by xylose. One would have been further motivated to link a nucleic acid molecule which encoded an antisense nucleic acid that inhibits the expression of a gene required for bacterial survival, in order to regulate the survival of a microbe of medical interest such as S. aureus, as disclosed by Ji et al. and Kernodle et al. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nancy T. Vogel whose telephone number is (571) 272-0780. The examiner can normally be reached on 7:00 - 3:30, Monday - Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Irem Yucel, Ph.D. can be reached on (571) 272-0781. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

NANCY VOGEL, PH.D.
PATENT EXAMINER